

Dorsal root ganglia sensory neuron transporters and their role in drug-induced neurotoxicity

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Drug transporters have been widely studied in cancer cells, mostly due to their importance in drug resistance. Given their clinical relevance, the role of drug transporters in chemotherapy-induced peripheral neurotoxicity (CIPN) is of particular interest, but knowledge is largely incomplete in dorsal root ganglia (DRG) sensory neurons. This critical aspect of CIPN has never been addressed until the observation in a single in vivo study that copper transporters are present and active in rat DRG neurons [1]. However, evidence is still missing regarding several crucial aspects of drug transporters, such as i) the possible co-localization of more than one transporter, ii) their relevance to each class of neurotoxic drugs, iii) their functionality and iv) the possibility to reduce toxicity through their pharmacological modulation in vivo.

The precise mechanisms of cellular uptake of DNA-intercalating platinum drugs are partly unknown, although it is commonly supposed that both passive diffusion as well as facilitated or active transport mechanisms play substantial roles. Cisplatin transporters suggested to be involved in modulation of platinum accumulation are MRP2, the copper transporters CTR1, ATP7A and ATP7B. Moreover, a recent notion is that various anticancer drugs can enter mammalian cells by facilitated transport via solute carriers (SLCs). Among all the SLCs transporters, organic cationic transporter 2 (OCT2) is a critical determinant in the uptake and cytotoxicity of cisplatin in non-neuronal cells, and its activity modulation has been associated with reduced toxicity [2].

The antitubulin alkaloid paclitaxel is a substrate of the energy-dependent drug efflux pump P-glycoprotein (P-gp). P-gp is a member of the ATP-binding cassette (ABC) family of transporters widely expressed in many human cancers and the enhanced efflux of paclitaxel has been observed in drug-resistant tumor cells that overexpress P-gp. The role of P-gp in paclitaxel efflux has been confirmed by employing membrane modulating agents (such as verapamil and cyclosporin A) in combination with paclitaxel. The distribution of this transporter in the central nervous system is well known, but it has never been investigated in peripheral neurons [1]. Recently, paclitaxel has also been recognized as a substrate for the copper transporter ATP7A.

The proteasome inhibitor bortezomib has only recently been described to be a substrate of ABCG2, another member of the ABC family, but only in human leukemia cells.

Other cellular transporters might also be implicated in neuronal damage in CIPN. We recently performed a thorough investigation on glutamate transporters derived from the observation that glutamate production inhibition reduced in rat models the neurotoxicity of cisplatin, paclitaxel and bortezomib [3]. We demonstrated the presence in the DRG of the transporters, their functionality and the possibility to modulate this functionality using pharmacological inhibitors (DL-threo- α -hydroxy-aspartate, dihydrokainate and L-serine-O-sulfate) in in vitro neuronal systems [4,5].

Preliminary results have already been obtained regarding OCT2 demonstrating the presence at the mRNA level and the possibility to modulate in vitro cisplatin cytotoxicity in DRG neurons using the transporter competitor cimetidine.

Based on these observations, the possible role of the different families of drug transporters and their possible relevance to CIP onset and severity will be here revised.

References

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